Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

A Unit of Scholars Academic and Scientific Society, India
www.saspublishers.com

Pediatrics

Study of Iron Deficiency Anemia - Risk Factor for Febrile Seizures

Dr. D. Chandraiah[1], Dr. B. Koteshwar[2*], Dr. Y. Sri Harsha[3], Dr. C. Suresh Kumar
[1]Associate Professor of Pediatrics, Government General Hospital, Nizamabad, India
[2]Associate Professor of Pediatrics, Niloufer Hospital, Hyderabad, India
[3]Post graduate in Pediatrics, Niloufer Hospital, Hyderabad, India
[4]Professors of Pediatrics, Niloufer Hospital, Hyderabad, India

Original Research Article

***Corresponding author**
Dr. B. Koteshwar

Article History
Received: 30.10.2018
Accepted: 07.11.2018
Published: 30.12.2018

DOI:
10.36347/sjams.2018.v06i12.007

Abstract: To study the association between iron deficiency and febrile seizures. To determine the hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin and serum ferritin level in children with febrile seizures and evaluating the role of iron deficiency in febrile seizures. To compare hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin and serum ferritin in cases and controls. This study is a case control study done in the department of pediatrics, Niloufer hospital. Study population was composed of 120 children out of which 60 were cases with febrile seizures and 60 were controls without febrile seizure. Children aged between 6 months to 5 years admitted to pediatric ward with febrile seizures were included in the case group. Control group is selected from age and sex matched children admitted with febrile illness more than 38 c but no serious and without iron supplements. A detailed history, general examination and systemic examination was carried out and complemented by laboratory investigations, estimation of hemoglobin, Red blood cell indices (MCV, MCH) and Serum ferritin. The mean age of cases is at presentation was 24.51 +/- 16.09 months and the mean age of controls was 24.83 +/- 15.14 months**.** Out of 60 cases of febrile seizures, 51 (85%) cases were simple febrile seizures and 9 (15%) were complex febrile seizures. 13 (21.6%) had family history of febrile seizure where as in controls there are 4 (6.6 %) children who had family history of febrile seizures. The hemoglobin levels were significantly lower in case group compared to control group. The present study concluded anemia as a risk factor for febrile seizures and emphasizes the importance of prevention and timely intervention and management of Iron deficiency anemia in children to decrease mortality and morbidity associated with febrile seizures.

Keywords: Anemia, Febrile Seizures, Hemoglobin, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, Serum Ferritin.

INTRODUCTION

Febrile seizures are the most common seizure disorder during childhood [1]. Febrile seizures are age dependent and are rare before 9 months and after 5 years of age. The peak onset being 14-18 months of age and the incidence approaches 3-4% of young children. Febrile seizures are frequently genetically determined. A strong family history of febrile convulsions in siblings and parents suggests genetic predisposition**.** Febrile convulsions occur in 2-5% of young children in North America and Europe and in 6-9% in Japan [2].

However there is a lack data regarding incidence of febrile seizures in Indian population. They are slightly more common in males. Few children will have a first episode after 3 years. It has been found that 21% children had a convulsion either before or within one hour of onset of fever, 57% between 1-24 hours after onset of fever and 22% had a convulsion more than 24 hours after onset of fever [3].

In 1980, a consensus conference held by the National Institutes of Health described a febrile seizure as, "An event in infancy or childhood usually occurring between three months and five years of age, associated with fever, but without evidence of intracranial infection or defined cause." It does not exclude children with prior neurological impairment and neither provides specific temperature criteria nor defines a seizure [4].

As iron is important for function of neurotransmitters [5] and various enzymes, low levels of serum ferritin [6] may lower seizure threshold. Fever can worsen the negative effect of low ferritin and may lower seizure threshold. Hence Iron deficiency is

postulated as possible risk factor for febrile seizures in children.

Aims and Objectives

- To study the association between iron deficiency and febrile seizures.
- To determine the hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin and serum ferritin level in children with febrile seizures and evaluating the role of iron deficiency in febrile seizures.
- To compare hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin and serum ferritin in cases and controls.

METHODOLOGY

Study conducted in Department of Pediatrics, Institute of Women and Child Health, Niloufer Hospital, Osmania Medical College, Hyderabad, over a period of One year from January 2016 to January 2017 and it is a case control study. Study population was composed of 120 children out of which 60 were cases with febrile seizures and 60 were controls without febrile seizure.

Inclusion criteria

All pediatric patients with febrile seizures between age group of 6 months to 5 years admitted in Niloufer hospital from January 2016 to January 2017.Those with febrile illness are taken as controls.

Exclusion criteria

- Children with CNS infection.
- Any other defined cause of seizures.
- Child with developmental delay.
- Child on iron therapy.
- Systemic metabolic abnormalities which produce seizures.
- Neurological Disorders.
- Neurodegenerative Disorders.

Methods of Collection of Data

Children presenting with febrile seizures were included in the case group and children who were admitted for other causes of fever were include in the control group. Written consent was taken from parents or guardians. A detailed history, general examination and systemic examination was carried out complemented by laboratory investigations for children aged between 6 months to 5 years admitted to pediatric ward with seizures. Control group is selected from age and sex matched children admitted with febrile illness more than 38^0C but no serious and without iron supplements. Investigations done were, estimation of hemoglobin, Red blood cell indices (MCV, MCH) and Serum ferritin

Iron deficiency was defined as hemoglobin less than 11 g/dl, MCV < 70 fl, MCH < 24 pg serum ferritin < 12 µg/dl. Since serum ferritin is acute phase reactant and its level is increased in any inflammatory conditions, in presence of fever a higher cut-off value of serum ferritin (30-60 microgram/dl) was considered. Case and controls were compared with respect to blood indices and serum ferritin. Estimation of hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin by auto analyzers and serum ferritin level by enhanced chemiluminescence immunoassay method is done.

All the observations were recorded and master chart was then created in Microsoft excel sheet. The qualitative values were transformed and were used for analysis. Statistical analysis was done using window stat version 8.6 statistical analyzer. Statistical data – t test applied. T value was chosen as the data was continuous and we wanted to find out significant differences between the two groups

RESULTS

The total no. of children 120 (n) was recruited in the study, out of which 60 were cases and 60 were controls.

Table-1: frequency distribution based on age and gender

Character	No	Age in M +/- SD	Male no	Male %	Female no	Female %
Case	60	24.51 +/- 16.09	35	58.3%	25	41.66%
Controls	60	24.83 +/- 15.14	39	65%	21	35%

Age of presentation

The age of the children included in our study varied from 6 – 60 months. The mean age of cases is at presentation was 24.51 +/- 16.09 months and the mean age of controls was 24.83 +/- 15.14 months. There is not much of difference in the gender percentage of both case and control group. The maximum numbers of children presented were below 2 years of age. (Fig.1)The numbers of males were slightly higher in controls than in the case group in our study but it is not statistically significant.

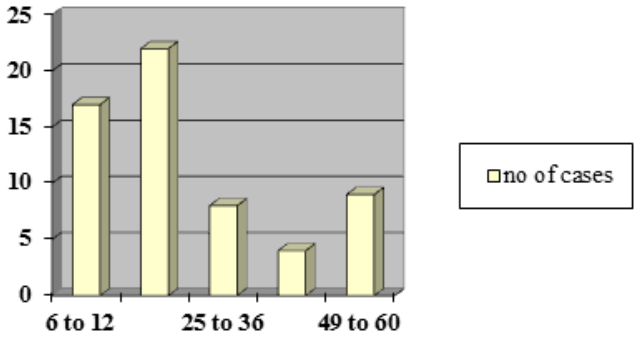

Fig-1: Age distribution among the cases in months

All the children who were included, a detailed history of the risk factors either in history, symptoms and signs which might point toward any underlying abnormality in laboratory parameter were asked. Most of the children the etiology of febrile illness was respiratory tract infections while other were viral infections. Out of 60 cases of children presenting with febrile seizures, 18 (30%) children had respiratory tract infection is the cause of fever at the time of presentation to emergency room. Out of 60 cases of febrile seizures, 51 (85%) cases were simple febrile seizures and 9 (15%) were complex febrile seizures. Out of 60 cases of febrile seizures, 13 (21.6%) had family history of febrile seizure where as in controls there are 4 (6.6 %) children who had family history of febrile seizures.

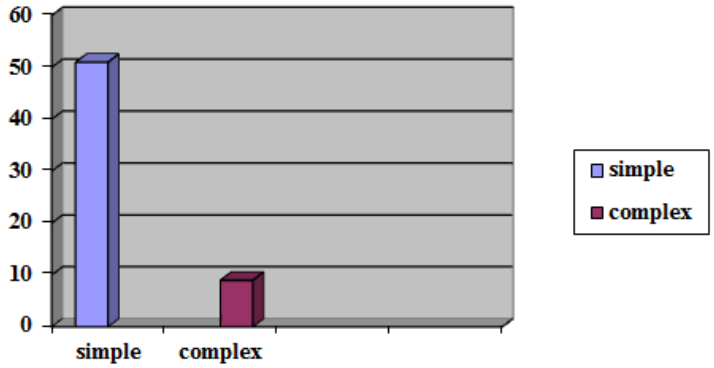

Fig-2: Type of febrile seizure in number

In our study the majority of febrile seizures were simple febrile seizures (85%) and others were complex febrile seizures (15%).Family history of febrile seizures was higher in the case group than in the control group, which suggests a role of genetic predisposition in the etiology of febrile seizures. There is family history of seizure disorder in 4 children of case group and in 3 children of control group. Degree of temperature was correlated in both the groups; the mean temperature of case group is 101.13 SD +/- 1.39 F, whereas the mean temperature of control group is 101.20 SD+/- 1.21 F. The temperature of control group is slightly higher than the case group. T test has been applied to correlate both the case and control group and the results are not significant (p = 0.7861).

T value for mean temperature comparison between case and control group is 0.2719 and it is not significant (p=0.786).

Table-2: Application of t test for case and control group temperatures in F

	Case	control	Pooled	SED	CD 95%	P value
N	60	60	120			
Mean	101.13	101.20	101.16	0.239	0.4374	
SD	1.393	1.219	0.239			0.7861
Standard error	0.1799	0.1574				
T test	0.2719					

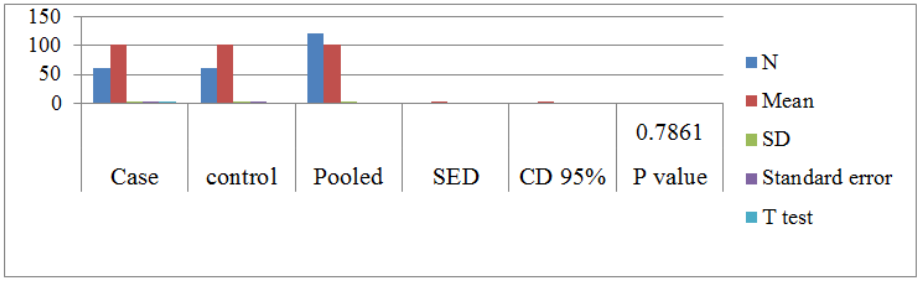

Fig-3

T test for comparison of hemoglobin between case and control group

The mean hemoglobin for case group is 10.87 SD+/- 1.577 gm% and the mean hemoglobin for the control group is 11.69 SD+/- 1.533 gm%. T test has been applied to find out the statistical significance between the case and control group.

Table-3: Application of test for case and control group Hemoglobin gm%

	Case	control	Pooled	SED	CD 95%	P value
N	60	60	120			0.0042
Mean	10.871	11.698	11.285	0.283	0.561	
SD	1.577	1.530	0.283			
Standard error	0.203	0.197				

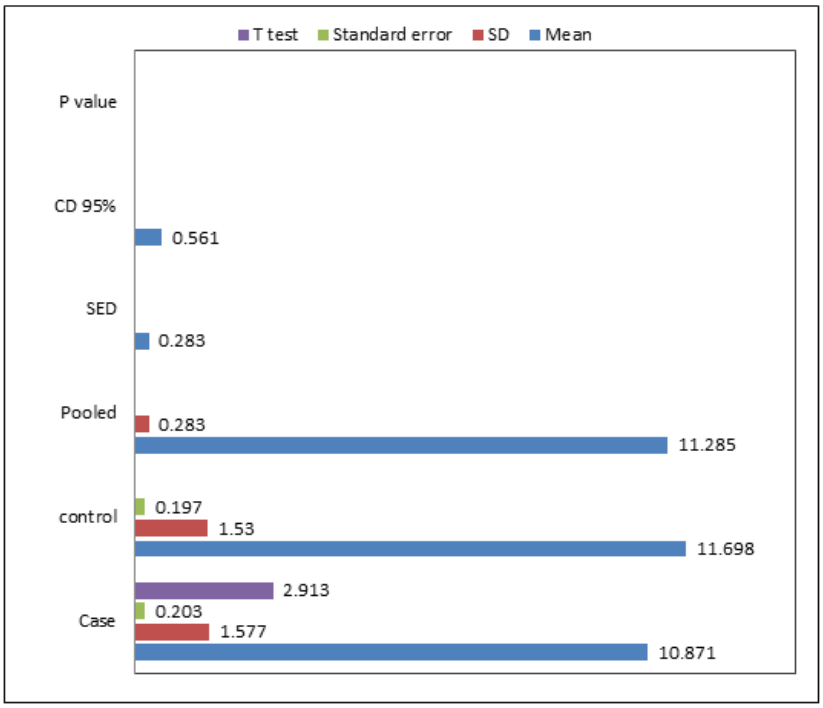

Fig-4

T value for hemoglobin is 2.913 and is statistically significant (p= 0.0042). The hemoglobin levels were significantly lower in case group compared to control group. Out of 60 cases 25(41.6%) children had hemoglobin less than 11 gm% whereas 12 (20%) children in controls had hemoglobin less than 11 gm%.

Comparison of Mean corpuscular volume between case and control group

The mean MCV of children with febrile seizures is 72.38 SD+/- 7.47 fl and the mean MCV in children without febrile seizures is 75.0633 SD+/- 5.507 fl. T test has been applied to find out the statistical difference between case and control group.

Table-4: Application of t test for case and control group MCV fl

	Case	control	Pooled	SED	CD 95%	P value
N	60	60	120			
Mean	72.381	75.063	73.722	1.198	2.273	
SD	7.474	5.507	1.198			0.0271
Standard error	0.964	0.711				
T test	2.2373					

T value for Mean corpuscular volume is 2.2373 and is statistically significant. The MCV of case group is lower when compared to control group. Out of 60 cases 23 (38.3%) children had Mean corpuscular volume less than 70 fl whereas 13(21.6%) children in control group had MCV less than 70 fl.

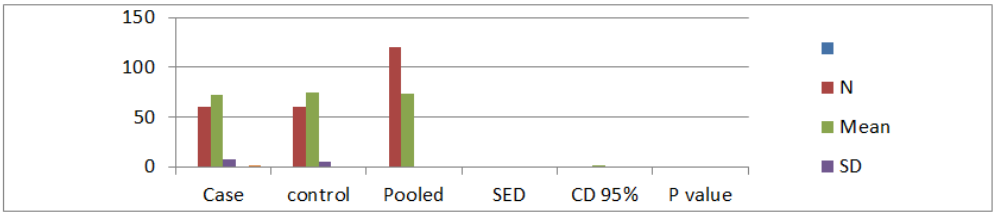

Fig-5

Comparison of Mean corpuscular hemoglobin between case and control group

The Mean corpuscular hemoglobin of case group is 26.311 SD+/- 3.233 and the Mean corpuscular hemoglobin of the control group is 27.896 SD+/- 2.165.T test has been applied to find out the statistical difference between the case and control groups.

Table-5: Application of t test for case and control group MCH pg

	Case	Control	Pooled	SED	CD 95%	P value
N	60	60	120			
Mean	26.311	27.896	27.104	0.502	0.995	
SD	3.233	2.165	0.502			0.0020
Standard error	0.417	0.279				
T test	3.154					

T test for Mean corpuscular hemoglobin by comparison between the case and control group is 3.154 and is statistically significant (p= 0.0020).The MCH is of case group is significantly lower when compared to the control group. Out of 60 cases 20 (33.3%) children had MCH less than 24pg where as in controls 10 (16.6%) children had MCH less than 24pg.

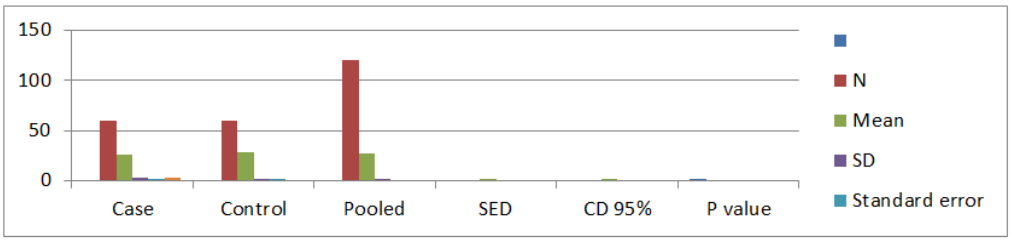

Fig-6

Comparison of Serum ferritin between case and control group

The mean serum ferritin of the case group is 58.271 SD +/- 28.29µg/l and the mean serum ferritin of the control group is 68.9233 SD+/- 25.32 µg/l. T test has been applied to find the statistical significance between the case and control group.

Table-6: Application of T test for case and control group serum ferritin µg/l

	Case	Control	Pooled	SED	CD 95%	P value
N	60	60	120			
Mean	58.271	68.923	63.597	4.902	9.70	
SD	28.29	25.32	4.902			0.0318
Standard error	3.65	3.269				
T test	2.172					

T test value for serum ferritin is 2.1728 and is statistically significant. P value is 0.0318.The serum ferritin of case group is significantly lower when compared to the control group.Since most of the children were having fever at the time of admission and as serum ferritin levels rise in acute inflammatory settings, a higher serum ferritin (30- 60 µg/l) cut off value is considered.Out of 60 cases,13 children (21.6 %) had very low serum ferritin < 30 µg/l where as in controls 3 (5%) children had serum ferritin less than 30 µg/l.

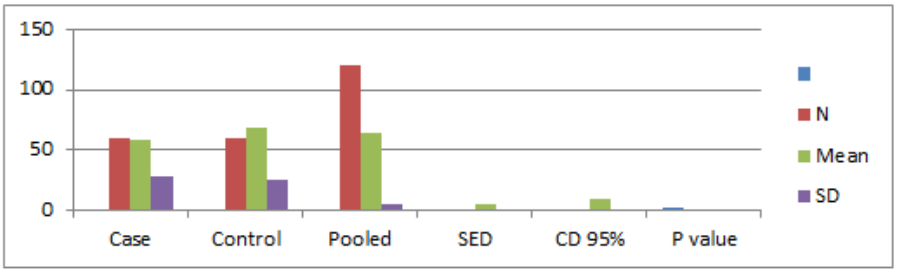

Fig-7

Table-7: Hematological parameters of cases and controls

Variable	case		Std.Err.	control		Std.Err.	T Test	Probability		Mann Whitney	Probability
Age Months	24.517	±	2.078	24.833	±	1.956	0.111	0.912		1724.000	0.346
Sex	1.417	±	0.064	1.350	±	0.062	0.746	0.457		1178.000	0.000
Weight kg	11.370	±	0.393	11.767	±	0.402	0.705	0.482		1656.000	0.226
Temperature F	101.137	±	0.180	101.202	±	0.157	0.272	0.786		1743.000	0.384
Hemoglobin gm%	10.872	±	0.204	11.698	±	0.198	2.914	0.004	**	1142.000	0.000
MCV Fl	72.382	±	0.965	75.063	±	0.711	2.237	0.027	*	1371.000	0.012
MCH Pg	26.312	±	0.417	27.897	±	0.280	3.155	0.002	**	1323.000	0.006
Serum Ferritin Micg/L	58.272	±	3.653	68.923	±	3.270	2.173	0.032	*	1340.000	0.008

DISCUSSION

Febrile convulsions are the most frequently occurring epilepsy syndrome (3- 4%) in children between 6 months and 5 years of age, but the incidence is as high as 15 percent in some populations. This incidence has been attributed to closer living arrangements among family members making detection more likely, but racial and geographic variations may also be important.

In the present study majority of cases were males (58.3%). This is in concurrence with general trend of febrile seizures. Most of the children presented were below 2 years. The risk of complex febrile convulsion increases if first fit occurs at a younger age. In our study 9(15%) children had complex febrile seizures and out of them 6(10%) occurred below 1 year. Al-Eissa *et al*. in1992 [8] and Farwell *et al*. in 1994[9] have also reported that age less than 12 months was related with increased incidence of complex febrile convulsions.

Both the case and control group were age and sex matched, so there is not much of difference to avoid age and gender bias. The mean age of case group is 24.51 +/- 16.09 months and the mean age of controls was 24.83 +/- 15.14 months. The percentage of males in case group is 58.3% and the percentage of males in control group is 65%. So there is not much of difference and is not statistically significant. In our study, majority of children had high grade fever at the presentation. The mean temperature of cases was 101.13 SD +/- 0.18 F and the mean temperature of children without febrile seizures was 101.20 SD+/- 0.15 F. There is no difference between the peak temperature of case and control group. In fact the mean temperature of children without febrile seizures was slightly higher than the children with febrile seizure. The finding argues against high fevers as a factor contributing to the severity of a

seizure. The most common cause of fever in our study leading to febrile convulsions was upper respiratory tract infections (30%). Rantala et al[10] in 1995 has also reported in their study that upper respiratory tract infection was the most common cause of fever (67%) in febrile convulsions.

A positive family history of febrile seizures points to the importance of genetic factors and common environmental exposures. In our study 13 (21.6%) children had positive family history of febrile convulsions. Tahir Saeed Siddiqui in 1981[11] has reported 20 percent of children with positive family history in his study. Farwel in 1994 reported positive family history in 29 percent of the cases. Thus the genetic contribution to incidence of febrile seizures is manifested by a positive family history for febrile seizures. In many families the disorder is inherited as an autosomal dominant trait, and multiple single genes causing the disorder have been identified. In most cases the disorder appears polygenic, and the genes predisposing to it remain to be identified.

In our study, most of the children (85%) had simple febrile seizures. Around 9 (15%) children came with complex febrile seizures. Among the children presenting with complex febrile seizures, 6(10%) children were less than 1 year of age suggesting that the incidence of complex febrile seizures is higher among the children presenting in less than 1 year of age.

Iron deficiency was defined as hemoglobin less than 11 g/dl, MCV < 70 fl, MCH < 24 pg serum ferritin < 12 µg/dl. Since serum ferritin is acute phase reactant and its level is increased in any inflammatory conditions, in presence of fever a higher cut-off value of serum ferritin (30-60 microgram/dl) was considered. Case and controls were compared with respect to blood indices and serum ferritin. Estimation of hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin by auto analyzers and serum ferritin level by enhanced chemiluminescence immunoassay method is done.

On laboratory investigation the mean hemoglobin for case group is 10.87 SD+/- 1.577 gm% and the mean hemoglobin for the control group is 11.69 SD+/- 1.533 gm%. Out of 60 cases 25(41.6%) children had hemoglobin less than 11 gm% whereas 12 (20%) children in control group had hemoglobin less than 11 gm%. T test for hemoglobin is 2.913 and is statistically significant (p= 0.0042). The hemoglobin levels were significantly lower in case group compared to control group.

The mean MCV of children with febrile seizures is 72.38 SD+/- 7.47 fl and the mean MCV in children without febrile seizures is 75.0633 SD+/- 5.507 fl. The MCV of case group is lower when compared to control group. Out of 60 cases 23 (38.3%) children had Mean corpuscular volume less than 70 fl whereas 13(21.6%) children in control group had MCV less than 70 fl. T value for Mean corpuscular volume is 2.2373 and is statistically significant (p = 0.02)

The Mean corpuscular hemoglobin of case group is 26.311 SD+/- 3.233 and the Mean corpuscular hemoglobin of the control group is 27.896 SD+/- 2.165. Out of 60 cases 20 (33.3%) children had MCH less than 24pg, where as in controls 10 (16.6%) children had MCH less than 24pg. T test for Mean corpuscular hemoglobin by comparison between the case and control group is 3.154 and is statistically significant (p = 0.0020). The MCH is of case group is significantly lower when compared to the control group.

Among all the above investigations, serum ferritin is more specific for iron deficiency. Since serum ferritin level increases in acute inflammatory settings and as most of the children in our study presented with high fever initially, a higher cut off value was considered (30-60 µg/l). A low serum ferritin less than 30 µg/l is almost definitive of iron deficiency.

The mean serum ferritin of the case group is 58.271 SD+/- 28.29 µg/l and the mean serum ferritin of the control group is 68.9233 SD+/- 25.32 µg/l. The serum ferritin of case group is significantly lower when compared to the control group. Out of 60 cases , 13 children (21.6 %) had very low serum ferritin < 30 µg/l where as in controls 3 (5%) children had serum ferritin less than 30 µg/l. T test value for serum ferritin is 2.1728 and is statistically significant. P value is 0.0318.

So as per this study there was definite association between iron deficiency and febrile seizures. The incidence of iron deficiency was significantly higher in the case group when compared to the control group. The levels of all the hematological parameters considered for diagnosing iron deficiency were significantly lower in the case group when compared to the control group. Leela Kumari *et al*. [13] did a case control ferritin study which concluded that iron deficiency is a significant risk factor for simple febrile seizures in children of age group 6 months to 3 years.

Ipisacane, *et al*. [14] did a case control study and concluded the study with the comment that low iron level is associated with febrile seizures and alternatively anemia can be associated with the severity of a febrile illness. Kobrinsky *et al*. [15] reported that iron deficiency raises the threshold for seizures in children. The main advantage of our study compared to the above studies is that we considered a higher cut off value for serum ferritin considering its rise in acute inflammatory settings.

Vaswani *et al.* also conducted a similar study with the observation of significantly low serum ferritin

levels in children with first febrile seizure than in controls. In 2009, Rajwanti K Vaswani [16] Praveen G D *et al*. conducted study which concluded that iron deficiency could be a potential risk factor for febrile seizure in children. The results of this study were also similar to our study underlying the importance of iron deficiency in children with febrile seizures. So as per our data we find iron deficiency as a risk factor for febrile seizures and there is significant association between iron deficiency and febrile seizures.

CONCLUSIONS

The present study conducted on 120 children of febrile seizures out of which 60 were cases and 60 were controls, concluded anemia as a risk factor for febrile seizures and emphasized the importance of preventing anemia and early detection and treatment of Iron deficiency anemia in children to prevent febrile seizures.

RECOMMENDATIONS

Prevention of anemia in children should start from antenatal period of mother by iron and folic acid supplementation along with iron rich foods. Mothers should be encouraged to give diet to children which are rich in iron. Information, Education and Communication media should take an active lead for wide propaganda for promoting the importance of taking iron rich foods which are commonly and cheaply available like Ragi, Green leafy vegetables and Jaggery every day in routine diet. Personal hygiene and de-worming also go a long to prevent worm infestation and subsequent anemia and febrile seizures.

REFERENCES

1. Johnston MV. Seizures in childhood: Febrile seizures. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson's Textbook of Pediatrics. 17thed. Pennsylvania: Saunders; 2004. p. 1994-1995.
2. Nelson KB, Ellenberg JH. Prenatal and perinatal antecedents of febrile seizures. Ann Neurol 1990;27:127-31.
3. Cassano PA, Koepsell TD, Farwell JR. Risk of febrile seizures in childhood in relation to prenatal maternal cigarette smoking and alcohol intake. Am J Epidemiol 1990;132:462-73.
4. Veena Kalra. Febrile Convulsions. In: Ghai OP, Gupta P, Paul VK, editors. Ghai Essential Pediatrics. 7th ed. New Delhi: CBS Publishers & Distributors; 2004.p. 528.
5. Gatti S, Vezzani A, Bartfai T. Mechanisms of fever and febrile seizures: putative role of the interleukin-1 system. In: Baram TZ, Shinnar S eds. *Febrile Seizures*. San Diego, Ca: Academic Press; 2002:169-88.
6. Haspolat S, Mihçi E, Coşkun M, Gümüslü S, Özbenm T, Yegin O. Interleukin-1β, tumor necrosis factor-α, and nitrite levels in febrile seizures. Journal of child neurology. 2002 Oct;17(10):749-51.
7. Iwasaki N, Nakayama J, Hamano K, Matsui A, Arinami T. Molecular genetics of febrile convulsion. Epilepsia 2002; 43 Suppl 9: 32-35.
8. YA al-Eissa Febrile seizures; rate and risk factors of recurrence J Child Neurol. 1995 jul;10(4):315-9.
9. Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures—effects on intelligence and on seizure recurrence. New England Journal of Medicine. 1990 Feb 8;322(6):364-9.
10. Rantala H, Uhari M, Hietala J. Factors triggering the first febrile seizure. Acta Paediatrica. 1995 Apr;84(4):407-10.
11. Siddiqui TS. Febrile convulsions in children: relationship of family history to type of convulsions and age at presentation. J Ayub Med Coll Abbottabad. 2002;14(4):26-8.
12. Hackett R, Hackett L, Bhakta P. Febrile seizures in a south Indian district: Incidence and associations. *Dev Med Child Neurol* 1997;39:380-4.
13. Sreeja S, Prashant TS, Leela C, Kumar VR, Tewari SP, Rao SV, Kiran PP. Effect of lens tilt on SCE and filamentation characteristics of femtosecond pulses in air. InNonlinear Optics and Applications VI 2012 May 11 (Vol. 8434, p. 84340T). International Society for Optics and Photonics.
14. Pisacane A, Sansone R, Impagliazzo N, Coppola A, Rolando P, D'Apuzzo A, Tregrossi C. Iron deficiency anaemia and febrile convulsions: case-control study in children under 2 years. British Medical Journal. 1996 Aug 10;313(7053):343-4.
15. Kobrinsky NL, Yager JY, Cheang MS, Yatscoff RW, Tenenbein M. Does iron deficiency raise the seizure threshold? J Child Neurol. 1995; 10: 105-109.
16. Rajwanti K Vaswani, Praveen G Dharaskar, Swati Kulkarni, K Ghosh. Iron deficiency as the first risk factor for febrile convulsion: Case control study in children between 6 months to 6 years. Indian pediatrics e-pub.2002.